

REMARKS

Claims 1-160 were pending. Upon entry of this amendment, claims 1, 21, and 157-161 will be pending. Accordingly, two (2) independent claims and six (6) dependent claims are pending.

This amendment cancels claims 2-20 and 22-156, replaces claims 1, 21, and 157-160 with correspondingly numbered claims, and adds new claim 161, support for which is found on page 38, lines 5-22 of the specification. No new matter has been added.

A version of the claims with markings to show where changes have been made appears in Appendix A at the end of this communication.

During a telephonic interview, the Examiner requested Applicants to re-provide pages 350-866 of the specification.

Accordingly, Applicants are pleased to provide the pages requested by the Examiner.

CONCLUSION

Allowance of claims 1, 21, and 157-161 is respectfully requested.



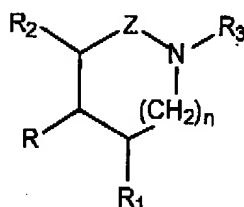
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Respectfully submitted,
Winn, et al.

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1 (Amended). A compound of the formula:

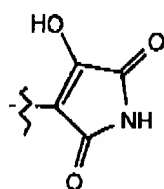


Z is -C(R₁₈)(R₁₉)- [or -C(O)-] wherein R₁₈ and R₁₉ are [independently selected from] hydrogen [and loweralkyl];

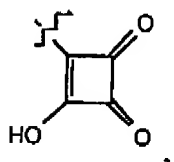
R is $-(\text{CH}_2)_m\text{-W}$ wherein m is [an integer from] 0 [to 6] and W is

- [(a)] $-\text{C}(\text{O})_2\text{-G}$ wherein G is hydrogen [or a carboxy protecting group,
- (b) $-\text{PO}_3\text{H}_2$,
- (c) $-\text{P}(\text{O})(\text{OH})\text{E}$ wherein E is hydrogen, loweralkyl or arylalkyl,
- (d) $-\text{CN}$,
- (e) $-\text{C}(\text{O})\text{NHR}_{17}$ wherein R_{17} is loweralkyl,
- (f) alkylaminocarbonyl,
- (g) dialkylaminocarbonyl,
- (h) tetrazolyl,
- (i) hydroxy,
- (j) alkoxy,
- (k) sulfonamido,
- (l) $-\text{C}(\text{O})\text{NHS}(\text{O})_2\text{R}_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,

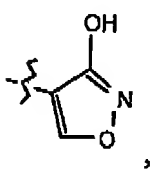
(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,



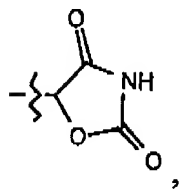
(n)



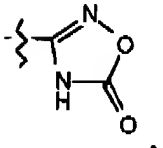
(o)



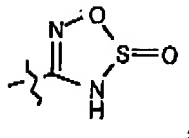
(p)



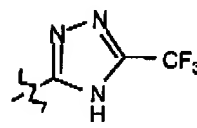
(q)



(r)

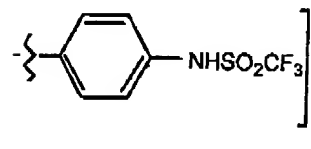


(s)



(t)

, or



(u)

R_1 and R_2 are independently selected from the group consisting of [hydrogen,] loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl,

haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ - wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene[, with the proviso that one or both of R_1 and R_2 is other than hydrogen]; and

R_3 is [(a)] $R_4-C(O)-R_5$ - [, R_4-R_{5a} -, $R_4-C(O)-R_5-N(R_6)$ - , $R_6-S(O)_2-R_7$ - or $R_{26}-S(O)-R_{27}$ -]

wherein R_5 is [(i) a covalent bond, (ii)] alkylene[, (iii) alkenylene, (iv) $-N(R_{20})-R_8$ - or $-R_{8a}-N(R_{20})-R_8$ -

wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene] and [alkenylene and

R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl or cycloalkylalkyl or

(v) $-O-R_9$ - or $-R_{9a}-O-R_9$ -

wherein R_9 and R_{9a} are independently selected from alkylene;

R_{5a} is (i) alkylene or (ii) alkenylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{21})-R_{10}$ - or $-R_{10a}-N(R_{21})-R_{10}$ -

wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;]

R_4 [and R_6 are independently] is selected from the group consisting of

(i) $(R_{11})(R_{12})N$ - wherein R_{11} is hydrogen and R_{12} [are independently]

is selected from the group consisting of

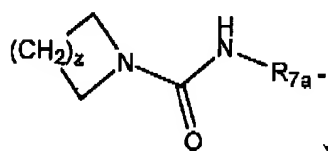
- [(1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl,
- (4) alkoxyalkyl,
- (5) haloalkoxyalkyl,
- (6) alkenyl,
- (7) alkynyl,
- (8) cycloalkyl,
- (9) cycloalkylalkyl,
- (10) aryl,
- (11) heterocyclic,
- (12)] arylalkyl,
- [(13) (heterocyclic)alkyl,
- (14) hydroxyalkyl,
- (15) alkoxy,
- (16) aminoalkyl,
- (17) trialkylaminoalkyl,
- (18) alkylaminoalkyl,
- (19) dialkylaminoalkyl,] and
- [(20) carboxyalkyl]

diarylalkyl

and

- (ii) [loweralkyl,
- (iii) alkenyl,
- (iv) alkynyl,
- (v) cycloalkyl,
- (vi) cycloalkylalkyl,
- (vii) aryl,
- (viii) arylalkyl,
- (ix) heterocyclic,
- (x) (heterocyclic)alkyl,

- (xi) alkoxyalkyl,
- (xii) hydroxyalkyl,
- (xiii) haloalkyl,
- (xiv) haloalkenyl,
- (xv) haloalkoxyalkyl,
- (xvi) haloalkoxy,
- (xvii) alkoxyhaloalkyl,
- (xviii) alkylaminoalkyl,
- (xix) dialkylaminoalkyl,
- (xx) alkoxy, and



(xxi)

wherein z is 0-5 and R_{7a} is alkylene;]

(R_{11a})(R_{12a})N-N(H)- wherein R_{11a} and R_{12a} are independently

selected from the group consisting of aryl and alkyl

[R₂₆ is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and

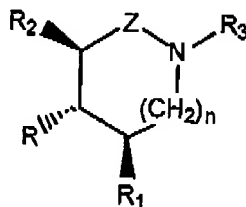
R₂₇ is alkylene or alkenylene;

- (b) R₂₂-O-C(O)-R₂₃- wherein R₂₂ is a carboxy protecting group or heterocyclic and R₂₃ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) -N(R₂₄)-R₂₅- wherein R₂₅ is alkylene and R₂₄ is hydrogen or loweralkyl,
- (c) loweralkyl,
- (d) alkenyl,
- (e) alkynyl,
- (f) cycloalkyl,
- (g) cycloalkylalkyl,

- (h) aryl,
- (i) arylalkyl,
- (j) aryloxyalkyl,
- (k) heterocyclic,
- (l) (heterocyclic)alkyl,
- (m) alkoxyalkyl,
- (n) alkoxyalkoxyalkyl, or
- (o) $R_{13}-C(O)-CH(R_{14})-$ wherein R_{13} is amino, alkylamino or dialkylamino and R_{14} is aryl or $R_{15}-C(O)-$ wherein R_{15} is amino, alkylamino or dialkylamino];

or a pharmaceutically acceptable salt thereof.

21 (Amended). The compound according to [C]claim 1 of the formula:



[wherein

Z is $-C(R_{18})(R_{19})-$ or $-C(O)-$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

n is 0 or 1;

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

- (a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,
- (b) $-PO_3H_2$,
- (c) $-P(O)(OH)E$ wherein E is hydrogen, loweralkyl or arylalkyl,
- (d) $-CN$,
- (e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,
- (f) alkylaminocarbonyl,
- (g) dialkylaminocarbonyl,

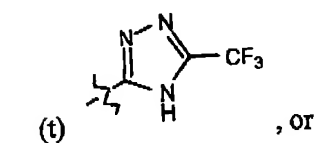
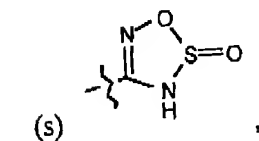
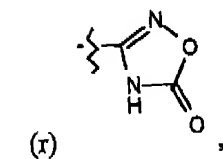
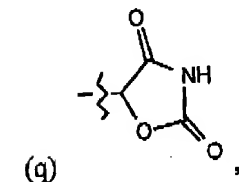
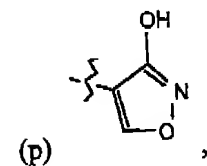
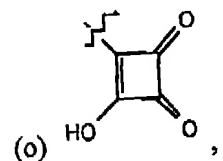
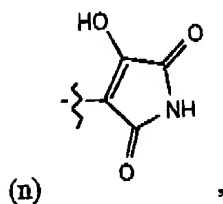
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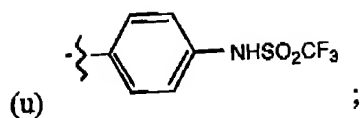
(h) tetrazolyl,

(i) hydroxy,

(j) alkoxy,

(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,



R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and (R_{aa})(R_{bb})N-R_{cc}- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is (a) R₄-C(O)-R₅-, R₄-R_{5a}-, R₆-S(O)₂-R₇- or R₂₆-S(O)-R₂₇-

wherein R₅ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) -N(R₂₀)-R₈- or -R_{8a}-

N(R₂₀)-R₈-

wherein R₈ and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and R₂₀ is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v) -O-R₉- or -R_{9a}-O-R₉-

wherein R₉ and R_{9a} are independently selected from alkylene;

R_{5a} is (i) alkylene or (ii) alkenylene;

R₇ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) -N(R₂₁)-R₁₀- or -R_{10a}-

N(R₂₁)-R₁₀-

wherein R₁₀ and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R₂₁ is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₄ and R₆ are independently selected from the group consisting of

(i) (R₁₁)(R₁₂)N- wherein R₁₁ and R₁₂ are independently selected from

(1) hydrogen,

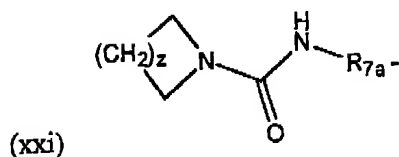
(2) loweralkyl,

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- (3) haloalkyl,
 - (4) alkoxyalkyl,
 - (5) haloalkoxyalkyl,
 - (6) alkenyl,
 - (7) alkynyl,
 - (8) cycloalkyl,
 - (9) cycloalkylalkyl,
 - (10) aryl,
 - (11) heterocyclic,
 - (12) arylalkyl,
 - (13) (heterocyclic)alkyl,
 - (14) hydroxyalkyl,
 - (15) alkoxy,
 - (16) aminoalkyl, and
 - (17) trialkylaminoalkyl,
-
- (ii) loweralkyl,
 - (iii) alkenyl,
 - (iv) alkynyl,
 - (v) cycloalkyl,
 - (vi) cycloalkylalkyl,
 - (vii) aryl,
 - (viii) arylalkyl,
 - (ix) heterocyclic,
 - (x) (heterocyclic)alkyl,
 - (xi) alkoxyalkyl,
 - (xii) hydroxyalkyl,
 - (xiii) haloalkyl,
 - (xiv) haloalkenyl,
 - (xv) haloalkoxyalkyl,
 - (xvi) haloalkoxy,
 - (xvii) alkoxyhaloalkyl,

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- (xviii) alkylaminoalkyl,
- (xix) dialkylaminoalkyl,
- (xx) alkoxy, and



wherein z is 0-5 and R_{7a} is alkylene;

R_{26} is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and

R_{27} is alkylene or alkenylene;

- (b) $R_{22}-O-C(O)-R_{23}-$ wherein R_{22} is a carboxy protecting group or heterocyclic and R_{23} is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{24})-R_{25}-$ wherein R_{25} is alkylene and R_{24} is hydrogen or loweralkyl,
- (c) loweralkyl,
- (d) alkenyl,
- (e) alkynyl,
- (f) cycloalkyl,
- (g) cycloalkylalkyl,
- (h) aryl,
- (i) arylalkyl,
- (j) aryloxyalkyl,
- (k) heterocyclic,
- (l) (heterocyclic)alkyl,
- (m) alkoxyalkyl,
- (n) alkoxyalkoxyalkyl, or
- (o) $R_{13}-C(O)-CH(R_{14})-$

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wherein R₁₃ is amino, alkylamino or dialkylamino and R₁₄ is aryl or R₁₅-C(O)-
 wherein R₁₅ is amino, alkylamino or dialkylamino;
 or a pharmaceutically acceptable salt thereof].

157 (Amended). [A] The compound according to claim 1 [of formula (I)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is aryl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from the group consisting of arylalkyl and diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is aryl].

158 (Amended). [A] The compound according to claim 1 [of formula (I)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is phenyl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from the group consisting of phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl].

159 (Amended). [A] The compound according to claim 21 [of formula (II)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is aryl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from the group consisting of arylalkyl and

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diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is aryl].

160 (Amended). [A] The compound according to claim 21 [of formula (II)] wherein [n is zero; Z is $-CH_2-$ wherein R_{18} and R_{19} are hydrogen; R is $C(O)-G$ wherein G is hydrogen;] R_1 is phenyl substituted with one substituent selected from the group consisting of methoxy, methoxyethoxy, and isopropoxyethoxy; R_2 is 1,3-benzodiox-5-yl; [R_3 is $R_4-C(O)-R_5$ wherein] R_5 is methylene; [and R_4 is selected from $(R_{11})(R_{12})N-$] and $[(R_{11a})(R_{12a})N-N(H)-$; one of R_{11} and] R_{12} is [hydrogen and the other is] selected from the group consisting of phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl].